UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION,

AND
TOXIC

PESTICIDES

SUBSTANCES

24/MAY/2005

MEMORANDUM

Subject:	Name of Pesticide Product:	RF2004 (CCSO)
	EPA Reg. No. /File Symbol:	2724-LNU
	DP Barcode:	D316836
	Decision No:	355865
	PC Codes:	105402, 128965

From: Eugenia McAndrew, Biologist
Technical Review Branch
Registration Division (7505C)

To: Bonaventure Akinlosotu, RM Team 13
Insecticide Branch
Registration Division (7505C)

Applicant: Wellmark International
1501 East Woodfield Road, Suite 200 West
Schaumburg, Illinois 60173

FORMULATION FROM LABEL:

	Active Ingredient:	% by wt.
105402	(S)-Methoprene	3.6
128965	Etofenprox	40.0
	Other Ingredients:	56.4
		Total: 100.0

ACTION REQUESTED: RM requests review of acute toxicity data for RF2004 (CCSO), EPA File Symbol 2724-LNU.

BACKGROUND: Wellmark International has submitted acute oral toxicity, acute dermal toxicity, primary eye irritation, primary skin irritation and dermal sensitization studies to support the registration of RF2004 (CCSO), EPA File Symbol 2724-LNU. The studies were conducted at Toxicology and Pharmacology, Ricerca Biosciences, Concord, Ohio with assigned MRID numbers 465134-04 to -08. The Registrant is requesting a waiver for the acute inhalation toxicity study requirement stating that the product is "a viscous liquid that is non-volatile and cannot be readily aerosolized."

RF2004 (CCSO) is a topical product for the control of adult fleas, flea eggs, flea larvae, adult ticks and repellency of mosquitoes on cats and kittens. A Companion Animal Safety Study (MRID 46513409) has been submitted for review.

RECOMMENDATIONS: The five studies have been reviewed and are classified as acceptable. A waiver is granted for the acute inhalation toxicity study.

The acute toxicity profile for RF2004 (CCSO), EPA File Symbol 2724-LNU, is as follows:

acute oral toxicity [a]	IV		Acceptable	MRID 46513404
acute dermal toxicity		IV	Acceptable	MRID 46513405
acute inhalation toxicity	IV		Waived	--
primary eye irritation		IV	Acceptable	MRID 46513406
primary skin irritation		IV	Acceptable	MRID 46513407
dermal sensitization		Negative	Acceptable	MRID 46513408

[a] The incorrect protocol (OECD 401: Acute Oral LD_{50}) was used for this test. Although, we accepted the study in this case, our guidance is that OECD 401 is an unacceptable protocol. Please inform the Registrant that the preferred protocol is OECD 425: Acute Oral Toxicity-Up-and-Down Procedure.

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System.

PRODUCT ID #: 002724-00504

PRODUCT NAME: RF2004 (CCSO)

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals:

SIGNAL WORD: CAUTION (optional)

First Aid: No statements are required. Registrant may use Category III statements.

The Registrant is also responsible for complying with PR Notice 96-6 which specifies statements that should be added to the labels of pesticide products which are registered for use on dogs and/or cats.

Reviewer: Eugenia McAndrew May 24, 2005

Risk Manager: 13

STUDY TYPE: Acute Oral Toxicity - S-D Rat; OPPTS 870.1100; OECD 401

TEST MATERIAL: RF2004 (CCSO) Lot # ED271; 3.55% (S)-Methoprene and 40.30% Etofenprox; liquid)

CITATION: Bassett, J. and Watson, M. Acute Oral Toxicity Study in Sprague-Dawley Rats with RF2004 (CCSO). Toxicology and Pharmacology Ricerca Biosciences, LLC, Concord, Ohio.
Laboratory Report Number 016063. September 30, 2004. MRID 46513404. Unpublished.

SPONSOR: Wellmark International, 1100 East Woodfield Road, Suite 500, Schaumburg, Illinois 60173

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46230704), 5/sex Crl:CD (SD) (IGS) BR strain young adult rats (Age: 9 weeks; Source: Charles River Laboratory, Inc., Portage, MI; 249-278 g males and 185-197 g females) were given a single oral dose of RF2004 (CCSO) Lot # ED271; 3.55% (S)-Methoprene and 40.30% Etofenprox; liquid) at a dose of 5010 mg/kg. Animals were then observed for 14 days.

Oral LD_{50} Males	> 5010 mg/kg
Oral LD_{50} Females	> 5010 mg/kg
Oral LD_{50} Combined	> 5010 mg/kg

All animals survived and gained weight. Clinical signs noted included few feces, hunched posture, excessive salivation and red material around the nose. Gross necropsy revealed bright yellow viscous fluid in the stomach of one male. No other gross abnormalities were observed.

Toxicity based on the lack of deaths at the limit dose. EPA Toxicity Category IV.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 401) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dosage (mg/kg bw)	Number of Deaths/Number Tested		
	Males	Females	Combined
5010	0/5	0/5	0/10

A. Mortality - none

B. Clinical observations - All animals gained weight. Clinical signs noted included few feces, hunched posture, excessive salivation and red material around the nose.

C. Gross Necropsy - Gross necropsy revealed bright yellow viscous fluid in the stomach of one male. No other gross abnormalities were observed.

D. Reviewer's Conclusions - We agree with the study author that RF2004 (CCSO) produced minimal toxicity when administered as a single oral gavage dose to rats.

Reviewer: Eugenia McAndrew May 24, 2005

Risk Manager: 13

STUDY TYPE: Acute Dermal Toxicity - NZW rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: RF2004 (CCSO) Lot # ED271; 3.55% (S)-Methoprene and 40.30% Etofenprox; liquid)

CITATION: Bassett, J. and Watson, M. Acute Dermal Toxicity Study in Sprague-Dawley Rats with RF2004 (CCSO). Toxicology and Pharmacology Ricerca Biosciences, LLC, Concord, Ohio.
Laboratory Report Number 016172. September 30, 2004. MRID 46513405. Unpublished.

SPONSOR: Wellmark International, 1100 East Woodfield Road, Suite 500, Schaumburg, Illinois 60173

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 4513405), 5/sex of Crl:CD (SD) (IGS) BR strain young adult rats (Age: 9 weeks; Source: Charles River Laboratory, Inc., Portage, MI; 281-305 g males and 201-206 g females) were dermally exposed to RF2004 (CCSO) Lot # ED271; 3.55% (S)-Methoprene and 40.30% Etofenprox; liquid). Five thousand ten mg/kg of the test substance was applied to a dose area of approximately 10% of the body surface area and covered with a porous gauze patch. The patch was wrapped with tape and bandaging around the trunk of each animal for a 24 hour period. The wrappings were removed and the test substance was wiped off the skin. Animals were then observed for 14 days.

Dermal LD_{50} Males > 5010 mg/kg bw
Dermal LD_{50} Females > 5010 mg/kg bw
Dermal LD_{50} Combined > 5010 mg/kg bw

All animals survived and gained weight. Clinical signs noted included red material around the nose or eyes and few or no feces. The animals recovered from these symptoms by day 3. No gross abnormalities were observed for any of the animals necropsied at the end of the study.

Toxicity based on the lack of deaths at the limit dose. EPA Toxicity Category IV.

This acute dermal study is classified acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dosage (mg/kg bw)	Number of Deaths/Number Tested		
	Males	Females	Combined
5010	0/5	0/5	0/10

A. **Mortality** - none

B. **Clinical observations** - All animals gained weight. Clinical signs noted included red material around the nose or eyes and few or no feces. The animals recovered from these symptoms by day 3.

C. **Gross Necropsy** - No gross abnormalities were observed.

D. **Reviewer's Conclusions** - We agree with the study author that RF2004 (CCSO) produced no systemic or dermal effects when applied dermally to rats.

Reviewer: Eugenia McAndrew May 24, 2005
Risk Manager: 13

STUDY TYPE: Primary Eye Irritation - NW Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: RF2004 (CCSO) Lot # ED271; 3.55% (S)-Methoprene and 40.30% Etofenprox; liquid)

CITATION: Bassett, J. and Watson, M. Acute Eye Irritation Study in New Zealand White Rabbits with RF2004 (CCSO). Toxicology and Pharmacology Ricerca Biosciences, LLC, Concord, Ohio. Laboratory Report Number 016174 . September 30, 2004. MRID 46513406. Unpublished.

SPONSOR: Wellmark International, 1100 East Woodfield Road, Suite 500, Schaumburg, Illinois 60173

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46513406), 0.1 mL of RF2004 (CCSO) Lot # ED271; 3.55% (S)-Methoprene and 40.30% Etofenprox; liquid) was instilled into the conjunctival sac of the right eye of three young adult New Zealand White female rabbits (Source: Covance Laboratory; Age: 13 weeks). The left eye served as the control. Animals were then observed at 1, 24, 48, 72 hours post-instillation. Irritation was scored by the method of Draize.

Conjunctivitis was noted in 2/3 eyes at the one hour observation. By 24 hours, all eyes were free of irritation.

In this study, formulation is minimally irritating. EPA Toxicity Category IV.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS AND DISCUSSION:

Observations	Number "positive"/number tested			
	Hours			
	1	24	48	72
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae:				
Redness	2/3	0/3	0/3	0/3
Chemosis	0/3	0/3	0/3	0/3
Discharge	0/3	0/3	0/3	0/3

*Score of 2 or more required to be considered "positive."

A. **Observations** - Conjunctivitis was noted in 2/3 eyes at the one hour observation. By 24 hours, all eyes were free of irritation.

B. **Reviewer's Conclusions:** We agree with the study author that RF2004 (CCSO) produced slight ocular irritation which reversed by 24 hours when applied to the eyes of rabbits.

Reviewer: Eugenia McAndrew May 24, 2005

Risk Manager: 13

STUDY TYPE: Primary Dermal Irritation - NW Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: RF2004 (CCSO) Lot # ED271; 3.55% (S)-Methoprene and 40.30% Etofenprox; liquid)

CITATION: Bassett, J. and Watson, M. Acute Dermal Irritation Study in New Zealand White Rabbits with RF2004 (CCSO). Toxicology and Pharmacology Ricerca Biosciences, LLC, Concord, Ohio. Laboratory Report Number 016173. September 30, 2004. MRID 46513407. Unpublished.

SPONSOR: Wellmark International, 1100 East Woodfield Road, Suite 500, Schaumburg, Illinois 60173

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46513407), three young adult New Zealand White female rabbits (Source: Covance Laboratory; Age: 12 weeks) were dermally exposed to RF2004 (CCSO) Lot # ED271; 3.55% (S)-Methoprene and 40.30% Etofenprox; liquid). Approximately 0.5 mL of the test material was applied to one 6 cm^2 intact dose site on each animal. Test sites were covered with a gauze patch and wrapped with semi-occlusive tape and bandaging for a period of 4 hours. The patches and bandaging were then removed and the skin was wiped clean. Animals were observed at 1, 24, 48 and 72 hours after patch removal. Irritation was scored by the method of Draize.

In this study, formulation is slightly irritating. EPA Toxicity Category IV.

Primary Dermal Irritation Index (PDII) = 0.5 All sites exhibited very slight to well defined erythema at the one hour observation resolving by 48 hours.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

A. Observations - All sites exhibited very slight to well defined erythema at the one hour observation resolving by 48 hours.

B. Results - PDII = 0.5

C. Reviewer's Conclusions - We agree with the study author that RF2004 (CCSO) produced slight dermal irritation which reversed by 48 hours when applied to the backs of rabbits

Reviewer: Eugenia McAndrew May 24, 2005

Risk Manager: 13

STUDY TYPE: Dermal Sensitization - Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: RF2004 (CCSO) Lot # ED271; 3.55% (S)-Methoprene and 40.30% Etofenprox; liquid)

CITATION: Bassett, J. and Watson, M. Dermal Sensitization Study (Closed-Patch Repeated Insult) in Guinea Pigs with RF2004 (CCSO). Toxicology and Pharmacology Ricerca Biosciences, LLC, Concord, Ohio. Laboratory Report Number 016175. November 18, 2001. MRID 46513408. Unpublished.

SPONSOR: Wellmark International, 1100 East Woodfield Road, Suite 500, Schaumburg, Illinois 60173

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46513408) with RF2004 (CCSO) Lot # ED271; 3.55% (S)-Methoprene and 40.30% Etofenprox; liquid), 30 young adult Hartley albino guinea pigs (Source: Elm Hill Breeding Labs, Chelmsford, MA; 316-398 g males and 330-384 g females) were tested using a modified Buehler design. The procedures were validated using 1-Chloro-2, 4-Dinitrobenzene (DNCB) as the positive control substance in a concurrent study.

During the induction phase, once each week for four weeks, 0.4 mL of the test substance was applied to the side of each animal for a 6-hour exposure period for a total of four exposures. A 50 % concentration of the test substance in distilled water was used for the first induction based on results of a range-finding study. Because the first induction was non-irritating, animals were dosed at higher concentrations for the subsequent induction doses. The dose for inductions 2 and 3 was 75% and induction 4 was 100%. (Induction 4 was added after consultation with the Sponsor.) Fourteen days after the last induction dose, 0.4 mL of a 12.5% concentration of the test substance in distilled water (the highest non-irritating concentration) was applied to a naive site on each test animal for a 6-hour challenge exposure. Ten naive control guinea pigs were also treated with the 12.5% concentration of the test substance in distilled water at challenge only. Readings were made 24 and 48 hours after each induction application and after the challenge application.

In this study, the formulation is not a dermal sensitizer.

For induction 1 (50%), no dermal scores were noted for any of the animals treated with the test material. At inductions 2 and 3 (75%), 3/20 animals exhibited very faint erythema (0.5 or ±). At induction 4 (100%, added after consultation with the Sponsor), 11/20 animals exhibited scores of ± or 1. Following the challenge, 3/20 test animals had scores of ± and 2/10 of the naive control animals had scores of ±. No positive scores were noted in either the test or naive control animals.
The results of the DNCB positive control study were appropriate to validate test procedures.

This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the Guinea pig.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. PROCEDURE

A. Induction - Once each week for four weeks, 0.4 mL of the test substance was applied to the side of each animal for a 6-hour exposure period for a total of four exposures. (Induction 4 was added after consultation with the Sponsor.) A 50 % concentration of the test substance in distilled water was used for the first induction based on results of a range-finding study. Because the first induction was non-irritating, animals were dosed at higher concentrations for the subsequent induction doses. The dose for inductions 2 and 3 was 75% and induction 4 was 100%. The animals rested for two weeks.

B. Challenge - Fourteen days after the last induction dose, 0.4 mL of a 12.5% concentration of the test substance in distilled water (the highest non-irritating concentration) was applied to a naive site on each test animal for a 6-hour challenge exposure.

C. Naive Controls - Ten naive control guinea pigs were also treated with the 12.5% concentration of the test substance in distilled water at challenge only.

II. RESULTS and DISCUSSION:

A. Reactions and duration - For induction 1 (50%), no dermal scores were noted for

any of the animals treated with the test material. At inductions 2 and 3 (75%), 3/20 animals exhibited very faint erythema (0.5 or ±). At induction 4 (100%, added after consultation with the Sponsor), 11/20 animals exhibited scores of ± or 1. Following the challenge, 3/20 test animals had scores of ± and 2/10 of the naive control animals had scores of ±. No positive scores were noted in either the test or naive control animals.

B. Positive control - The results of the DNCB positive control study were appropriate to validate test procedures.

C. Reviewer's Conclusions: We agree with the study author that RF2004 (CCSO) produced minimal irritation. None of the test group animals responded with a higher skin grade than the control animals. The test material is considered a non-sensitizer.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D316836
2. **PC CODES:** 105402, 128965
3. **CURRENT DATE:** 24/MAY/2005
4. **TEST MATERIAL:** RF2004 (CCSO) Lot # ED271; 3.55% (S)-Methoprene and 40.30% Etofenprox; liquid)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Toxicology and Pharmacology Ricerca Biosciences, LLC 016063/9-30-04	46230704	LD_{50} > 5010 mg/kg (males, females combined)	IV	A
Acute dermal toxicity/rat Toxicology and Pharmacology Ricerca Biosciences, LLC 016172/9-30-04	46513405	LD_{50} > 5010 mg/kg (males, females combined)	IV	A
Acute inhalation toxicity	--	Study waived	IV	W
Primary eye irritation/rabbit Toxicology and Pharmacology Ricerca Biosciences, LLC 016174/9-30-04	46513406	Conjunctivitis in 2/3 eyes resolving by 24 hours	IV	A
Primary dermal irritation/rabbit Toxicology and Pharmacology Ricerca Biosciences, LLC 016173/9-30-04	46513407	PDII = 0.5 No irritation at 48 hours	IV	A
Dermal sensitization/guinea pig Toxicology and Pharmacology Ricerca Biosciences, LLC 016175/11-18-01	46513408	Not a sensitizer	–	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived**